PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 221/00, 401/10, A61K 31/44, C07D 491/04 | A1

(11) International Publication Number: WO 99/05111

(43) International Publication Date: 4 February 1999 (04.02.99)

(21) International Application Number: PCT/EP98/04477

(22) International Filing Date: 18 July 1998 (18.07.98)

(30) Priority Data:
97112792.3 25 July 1997 (25.07.97) EP

(71) Applicant *(for all designated States except US)*: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE).

(72) Inventors *(for all designated States except CA US)*: AMSCHLER, Hermann; Hohenhewenstrasse 19, D-78315 Radolfzell (DE). FLOCKERZI, Dieter; Ackerweg 26, D-78476 Allensbach (DE). ULRICH, Wolf-Rüdiger; Hebelstrasse 3, D-78464 Konstanz (DE). BÄR, Thomas; Blarerstrasse 16, D-78462 Konstanz (DE). MARTIN, Thomas; Sonnenbühlstrasse 73, D-78464 Konstanz (DE). SCHUDT, Christian; Schützenstrasse 20, D-78462 Konstanz (DE). HATZELMANN, Armin; Alter Wall 3, D-78467 Konstanz (DE). BEUME, Rolf; Bohlstrasse 13, D-78465 Konstanz (DE). HÄFNER, Dietrich; Beethovenstrasse 5, D-78464 Konstanz (DE). BOSS, Hildegard; Flurweg 3a, D-78464 Konstanz (DE). KLEY, Hans-Peter; Im Weinberg 3b, D-78476 Allensbach (DE).

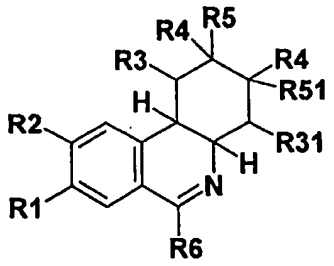
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: GUTTERER, Beate [DE/DE]; Allensbacher Strasse 6b, D-78476 Allensbach (DE).

(74) Common Representative: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE).

(81) Designated States: AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NOVEL TETRAZOLE DERIVATIVES



(I)

(57) Abstract

Compounds of formula (I) in which R1, R2, R3, R31, R4, R5, R51 and R6 have the meanings indicated in the description, are novel efficacious bronchial therapeutics.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Novel tetrazole derivatives

Field of application of the invention

The invention relates to novel 6-[(tetrazol-5-yl)-phenyl]phenanthridines, which are used in the pharmaceutical industry for the production of medicaments.

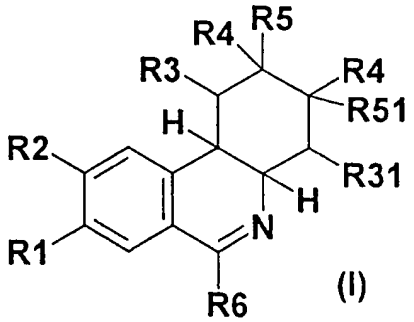
Known technical background

Chem. Ber. **1939**, 72, 675-677, J. Chem. Soc., **1956**, 4280-4283 and J. Chem. Soc. (C), **1971**, 1805 describe the synthesis of partial hydrogenated 6-phenylphenanthridines. In the international patent applications WO97/35854 and WO97/28131 partial hydrogenated 6-phenylphenanthridines are described as cyclic nucleotide phosphodiesterase (PDE) inhibitors of type 4.

Description of the invention

It has now been found that the novel 6-phenyl-phenanthridines, which are described below in greater detail, which differ from the prior art, in particular, by the substitution on the 6-phenyl ring, have surprising and particularly advantageous properties.

The invention thus relates to compounds of the formula I



(I)

in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-2C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,

R31 is hydrogen or 1-4C-alkyl,

or in which

R3 and R31 together are a 1-4C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together are an additional bond,

R6 is a phenyl radical substituted by R7, where

R7 is a tetrazol-5-yl radical substituted by a radical R8, where

R8 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl or Ar-1-4C-alkyl, where

Ar is a phenyl radical which is unsubstituted or substituted by R9 and/or R10, and

R9 and R10 independently of one another are halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl or 1-4C-alkoxy,

and the salts of these compounds.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and, preferably, the ethyl and methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and, preferably, the ethoxy and methoxy radicals.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy represents cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

Completely or predominantly fluorine-substituted 1-4C-alkoxy which may be mentioned are, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular

the 1,1,2,2-tetrafluoroethoxy, the trifluoromethoxy, the 2,2,2-trifluoroethoxy and, preferably, the difluoromethoxy radicals. "Predominantly" in this connection means that more than half of the hydrogen atoms are substituted by fluorine atoms.

1-2C-Alkylenedioxy represents, for example, the methylenedioxy (-O-CH_2-O-) and the ethylenedioxy radicals (-O-CH_2-CH_2-O-).

If R3 and R31 together have the meaning 1-4C-alkylene, the positions 1 and 4 in compounds of the formula I are linked to one another by a 1-4C-alkylene bridge, 1-4C-alkylene representing straight-chain or branched alkylene radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the radicals methylene (-CH_2-), ethylene (-CH_2-CH_2-), trimethylene (-CH_2-CH_2-CH_2-), 1,2-dimethylethylene [-CH(CH_3)-CH(CH_3)-] and isopropylidene [-C(CH_3)$_2$-].

If R5 and R51 together are an additional bond, then the carbon atoms in positions 2 and 3 in compounds of the formula I are linked to one another via a double bond.

1-7C-Alkyl represents straight-chain or branched alkyl radicals having 1 to 7 carbon atoms. Examples which may be mentioned are the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

3-7C-Cycloalkyl represents the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the cycloheptyl radicals. The 5-7C-cycloalkyl radicals cyclopentyl, cyclohexyl and cycloheptyl may be mentioned as preferred.

3-7C-Cycloalkylmethyl represents a methyl radical which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopentylmethyl and the cyclohexylmethyl radicals.

Ar-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the aryl radicals defined above. Examples which may be mentioned are the p-methoxybenzyl, the phenethyl and the benzyl radicals.

Halogen within the meaning of the invention is bromine, chlorine and fluorine.

Suitable salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the

inorganic and organic acids and bases customarily used in pharmacy. Those which are suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are employed in salt preparation - depending on whether it is a mono- or polybasic acid and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand - for example if the tetrazol-5-yl radical R7 is substituted by R8=H - salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminum, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts which may be obtained initially as process products, for example in the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

Compounds of the formula I to be emphasized are those in which

R1 is 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

or in which

R3 and R31 together are a 1-2C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together are an additional bond,

R6 is a phenyl radical substituted by R7, where

R7 is a tetrazol-5-yl radical substituted by a radical R8, where

R8 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl or Ar-1-4C-alkyl, where

Ar is a phenyl radical which is unsubstituted or substituted by R9 and/or R10, and

R9 and R10 independently of one another are 1-4C-alkyl or 1-4C-alkoxy,

and the salts of these compounds.

Compounds of the formula I particularly to be emphasized are those in which

R1 is 1-4C-alkoxy, 3-7C-cycloalkoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-4C-alkoxy, 3-7C-cycloalkoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

or in which

R3 and R31 together are a 1-2C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together are an additional bond,

R6 is a phenyl radical substituted by R7, where

R7 is a tetrazol-5-yl radical substituted by a radical R8, where

R8 is hydrogen, 1-4C-alkyl, 5-7C-cycloalkyl, 3-7C-cycloalkylmethyl or Ar-1-2C-alkyl, where

Ar is a phenyl radical which is unsubstituted or substituted by R9, and

R9 is 1-2C-alkyl or 1-2C-alkoxy,

and the salts of these compounds.

Preferred compounds of the formula I are those in which

R1 is 1-4C-alkoxy,

R2 is 1-4C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is hydrogen,

R5 is hydrogen,

R51 is hydrogen,

R6 is a phenyl radical substituted by R7, where

R7 is a tetrazol-5-yl radical substituted by R8, where

R8 is hydrogen, 1-4C-alkyl or 4-methoxybenzyl,

and the salts of these compounds.

Particularly preferred compounds of the formula I are those in which

R1 is methoxy or ethoxy,

R2 is methoxy or ethoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is hydrogen,

R5 is hydrogen,

R51 is hydrogen,

R6 is a phenyl radical substituted by R7, where

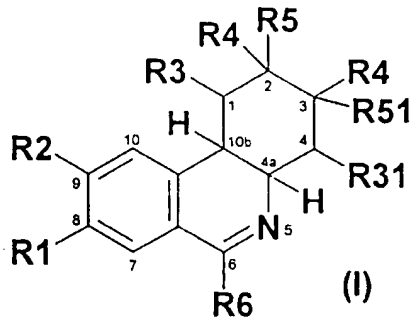
R7 is a 2H-tetrazol-5-yl radical substituted by R8, where

R8 is hydrogen, ethyl or 4-methoxybenzyl,

and the salts of these compounds.

The compounds of the formula I are chiral compounds having chiral centers in the positions 4a and 10b and, depending on the meaning of the substituents R3, R31, R4, R5 and R51, further chiral centers in the positions 1, 2, 3 and 4.

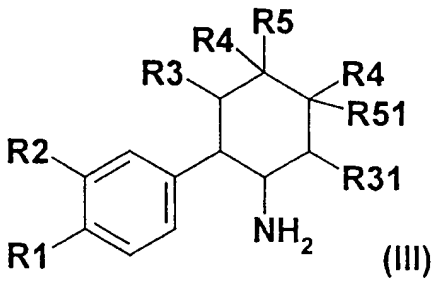
Numbering:



(I)

The invention therefore includes all conceivable pure diastereomers and pure enantiomers and their mixtures in any mixing ratio, including the racemates. The compounds of the formula I are preferred in which the hydrogen atoms in the positions 4a and 10b are cis to one another. Particularly preferred here are the pure cis-diastereomers and the pure cis-enantiomers and their mixtures in any mixing ratio and including the racemates.

The enantiomers can be separated in a manner known per se (for example by preparation and separation of appropriate diastereoisomeric compounds). Preferably, a separation of enantiomers takes place at the stage of the starting compounds of the formula III



(III)

for example via salt formation of the racemic compounds of the formula III with optically active carboxylic acids. Alternatively, enantiomerically pure starting compounds of the formula III can also be prepared via asymmetric syntheses.

The tetrazol-5-yl radical R7 of the compounds of the formula I can be bonded to the phenyl radical R6 either in the ortho, meta or para position to the phenanthridine ring.

Those compounds of the formula I are preferred in which the tetrazol-5-yl radical R7 is bonded to the phenyl radical R6 in the meta or para position to the phenanthridine ring. The compounds of the formula I in which the tetrazol-5-yl radical R7 is bonded in the para position are particular preferred in this connection.

Compounds of the formula I in which R1, R2, R3, R31, R4, R5, R51, R6 and R7 have the meanings indicated above and R8 is hydrogen occur in 2 tautomeric forms, which are in equilibrium with one another (1H and 2H form of the tetrazol-5-yl radical). The invention therefore includes both tautomeric forms in any mixing ratio.

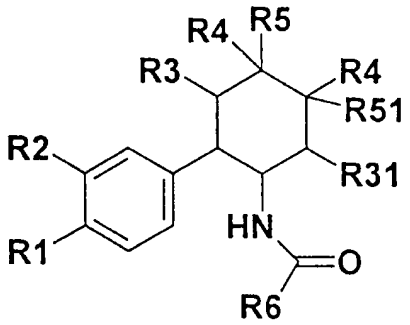
By bonding of the substituent R8 (R8≠H) to the tetrazol-5-yl group, the conversion of the two tautomeric forms into one another is blocked. The invention therefore also relates to the 1H- and 2H-tetrazol-5-yl compounds of the formula I substituted by a radical R8 (R8≠H), both in pure form and in any mixing ratio. In this connection, the compounds of the formula I are preferred in which the tetrazol-5-yl radical is substituted in the 2 position by one of the radicals R8 (R8≠H).

The invention further relates to a process for the preparation of the compounds of the formula I, in which R1, R2, R3, R31, R4, R5, R51, A and R6 have the meanings indicated above, and their salts.

The process comprises

a) for the preparation of compounds of the formula I in which R1, R2, R3, R31, R4, R5, R51, R6 and R7 have the meanings indicated above and R8 is hydrogen, reacting corresponding compounds of the formula I, in which R6 is cyanophenyl, with alkali metal azides and halogen salts of ammonia, or

b) for the preparation of compounds of the formula I in which R1, R2, R3, R31, R4, R5, R51, R6, R7 and R8 (R8≠H) have the meanings indicated above, cyclocondensing corresponding compounds of the formula II



(II)

and,

if desired, then converting the compounds of the formula I obtained according to a) or b) into their salts, or, if desired, then converting salts of the compounds of the formula I obtained according to a) or b) into the free compounds.

If desired, compounds of the formula I obtained can be converted into further compounds of the formula I by derivatization. For example, compounds of the formula I in which R6 is a phenyl radical substituted by R7 and R7 is an unsubstituted 1H- or 2H-tetrazol-5-yl radical can be converted into the corresponding substituted tetrazole compounds of the formula I by alkylation reactions, the hydrogen on the tetrazole ring being replaced by the radicals mentioned for R8 - excluding hydrogen. The reactions are expediently carried out analogously to the methods known to the person skilled in the art, e.g. by reaction of the 1H- or 2H-tetrazole compounds of the formula I with compounds of the formula R8-X in the presence of a base, R8 having the abovementioned meanings - excluding hydrogen - and X being a suitable leaving group such as, for example, a chlorine, bromine or iodine atom or an alkylsulfate radical. The 1- and 2-substituted tetrazole regioisomer mixtures usually formed in the alkylation are separated by methods known to the person skilled in the art, such as

crystallization or chromatography on suitable support materials. An analogous alkylation of tetrazoles and separation of the regioisomers is described, for example, in J. Med. Chem. **1996**, 39, 2354.

The reaction of cyanophenyl derivatives with alkali metal azides and halogen salts of ammonia to give 2-, 3- or 4-(1H- or 2H-tetrazol-5-yl)phenyl derivatives which are unsubstituted in the tetrazole moiety is described, for example, in J. Med. Chem. **1993**, 36, 3246.

Cyclocondensation is carried out in a manner known per se to the person skilled in the art according to Bischler-Napieralski (e.g. as described in J. Chem. Soc., **1956**, 4280-4282) in the presence of a suitable condensing agent, such as, for example, polyphosphoric acid, phosphorus pentachloride, phosphorus trichloride, phosphorus pentoxide, thionyl chloride or preferably phosphorus oxychloride, in a suitable inert solvent, e.g. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as acetonitrile, or without further solvent using an excess of condensing agent, preferably at elevated temperature, in particular at the boiling temperature of the solvent or condensing agent used.

Compounds of the formula II, in which R1, R2, R3, R31, R4, R5, R51 and R6 have the meanings indicated above, are accessible from the corresponding compounds of the formula III, in which R1, R2, R3, R31, R4, R5 and R51 have the meanings indicated above, by reaction with compounds of the formula R6-CO-X, in which R6 has the meaning indicated above and X is a suitable leaving group, preferably a chlorine atom. For example, benzoylation is carried out as in the following examples according to the Einhorn process, the Schotten-Baumann variant or as described in J. Chem. Soc. (C), **1971**, 1805-1808.

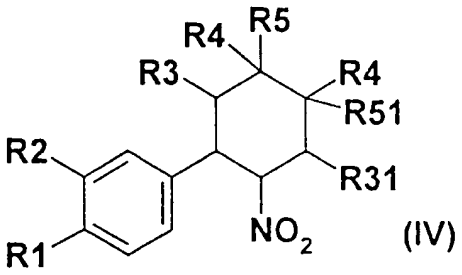
Compounds of the formula R6-CO-X and compounds of the formula III are either known or can be prepared in a known manner.

Compounds of the formula R6-CO-X can be prepared, for example, from the corresponding carboxylic acids R6-COOH, in which R6 has the meaning indicated above, by reaction in a manner familiar to the person skilled in the art.

The compounds R6-COOH, in which R6 has the meaning indicated above, are either known or can be obtained from alkyl 2-, 3- or 4-cyanobenzoates in a manner known to the person skilled in the art, e.g. by reaction with alkali metal azides and halogen salts of ammonia to give alkyl 2-, 3- or 4-(1H- or 2H-tetrazol-5-yl)benzoates which are unsubstituted in the tetrazole moiety. Such a reaction is described, for example, in J. Med. Chem. **1993**, 36, 3246. If desired, these intermediates can be converted by alkylation with compounds of the formula R8-X in the presence of a base - as described above for the

1H- or 2H-tetrazole compounds of the formula I or in the abovementioned literature - into alkyl R6-carboxylates, in which R6 is a phenyl radical substituted by R7, R7 is a 1H- or 2H-tetrazol-5-yl radical substituted by a radical R8 and R8 is not hydrogen, but has one of the other abovementioned meanings for R8. By means of alkaline or acidic hydrolysis conditions familiar to the person skilled in the art, the alkyl R6-carboxylates are converted into the free carboxylic acids R6-COOH.

The compounds of the formula III can be prepared, for example, from compounds of the formula IV



(IV)

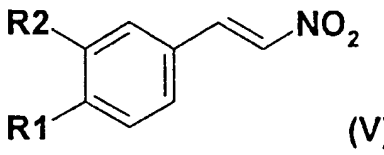
in which R1, R2, R3, R31, R4, R5 and R51 have the meanings mentioned above, by reduction of the nitro group.

Reduction is carried out in a manner known to the person skilled in the art, for example as described in J. Org. Chem. **1962**, 27, 4426 or as described in the following examples. Preferably, reduction is carried out by catalytic hydrogenation, e.g. in the presence of Raney nickel, in a lower alcohol such as methanol or ethanol at room temperature and under normal or elevated pressure. If desired, a catalytic amount of an acid, such as, for example, hydrochloric acid, can be added to the solvent.

The compounds of the formula III, in which R1, R2, R3, R31 and R4 have the meanings indicated above and R5 and R51 together are an additional bond, can be prepared from the corresponding compounds of the formula IV by selective reduction of the nitro group in a manner known to the person skilled in the art, for example in the presence of Raney nickel in a lower alcohol as a solvent using hydrazine hydrate as a hydrogen donor.

The compounds of the formula IV, in which R1, R2, R3, R31 and R4 have the meanings indicated above and R5 and R51 are hydrogen, are either known or can be prepared from corresponding compounds of the formula IV, in which R5 and R51 together are an additional bond. The reaction can be carried out in a manner known to the person skilled in the art, preferably by hydrogenation in the presence of a catalyst, such as, for example, palladium on activated carbon, e.g. as described in J. Chem. Soc. (C), **1971**, 1805-1808.

The compounds of the formula IV, in which R5 and R51 together are an additional bond, are either known or can be obtained by reaction of compounds of the formula V



(V)

in which R1 and R2 have the abovementioned meanings, with compounds of the formula VI

R3-CH=C(R4)-C(R4)=CH-R31 (VI)

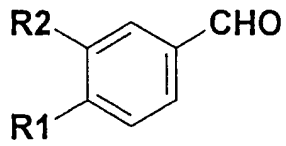
in which R3, R31 and R4 have the abovementioned meanings.

Cycloaddition is carried out here in a manner known to the person skilled in the art according to Diels-Alder, e.g. as described in J. Amer. Chem. Soc. **1957**, 79, 6559 or in J. Org. Chem. **1952**, 17, 581 or as described in the following examples.

Compounds of the formula IV obtained in the cycloaddition, in which the phenyl ring and the nitro group are trans to one another, can be converted into the corresponding cis compounds in a manner known to the person skilled in the art, e.g. as described in J. Amer. Chem. Soc. **1957**, 79, 6559 or as described in the following examples.

The compounds of the formula V and VI are either known or can be prepared in a known manner. The compounds of the formula V can be prepared, for example, from corresponding compounds of the formula VII in a manner known to the person skilled in the art, as described, for example, in J. Chem. Soc. **1951**, 2524 or in J. Org. Chem. **1944**, 9, 170 or as in the following examples.

The compounds of the formula VII



(VII)

in which R1 and R2 have the meanings indicated above, are either known or can be prepared in a manner known to the person skilled in the art, as described, for example, in Ber. Dtsch. Chem. Ges. **1925**, 58, 203.

The isolation and purification of the substances according to the invention are carried out in a manner known per se, for example by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example column chromatography on suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent, e.g. in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol (ethanol, isopropanol), which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitation, precipitation with a nonsolvent for the addition salt or by evaporation of the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this manner, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

The following examples serve to explain the invention in greater detail without restricting it. Likewise, further compounds of the formula I whose preparation is not described explicitly can be prepared in an analogous manner or in a manner familiar to the person skilled in the art using customary process techniques.

In the examples, m.p. stands for melting point, h for hour(s), RT for room temperature, EF for empirical formula, MW for molecular weight, calc. for calculated, fnd for found. The compounds and their salts mentioned in the examples are a preferred subject of the invention.

Examples

Final products

1. **(+/-)-cis-9-Ethoxy-8-methoxy-6-[4-(2H-tetrazol-5-yl)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridine**

4.2 g of (+/-)-cis-9-ethoxy-8-methoxy-6-(4-cyano-phenyl)-1,2,3,4,4a,10b-hexahydrophenanthridine (compound A1), 0.65 g of ammonium chloride and 0.83 g of sodium azide are suspended in 150 ml of abs. dimethylformamide and heated at 120°C for 24 h. The reaction mixture is partitioned between water and diethyl ether, and the organic phase is dried with sodium sulfate and concentrated. The residue is chromatographed on silica gel using methylene chloride/methanol in the ratio 4/1. After concentration of the corresponding eluate fractions, the title compound is obtained as a solidified oil.

EF: $C_{23}H_{25}N_5O_2$; MW 403.48

Elemental analysis x 0.7 H_2O:	calc.:	C 66.39	H 6.40	N 16.83
	fnd:	C 66.34	H 6.46	N 16.45

2. **(+/-)-cis-9-Ethoxy-8-methoxy-6-[4-(2-ethyl-2H-tetrazol-5-yl)phenyl]-1,2,3,4,4a,10b-hexa-hydrophenanthridine**

3.55 g of (+/-)-cis-N-[2-(3-ethoxy-4-methoxyphenyl)-cyclohexyl]-4-(2-ethyl-2H-tetrazol-5-yl)benzamide (compound A2) are dissolved in 150 ml of acetonitrile and 1.0 ml of phosphorus oxychloride and the solution is stirred at 80°C overnight. The reaction mixture is treated with 60 ml of ethyl acetate and extracted with sodium hydrogencarbonate solution. The organic phase is dried using sodium sulfate and concentrated. The residue is extracted by stirring with ethyl acetate/petroleum ether in the ratio 1/1, filtered off with suction and dried. 2.06 g of the title compound of m.p. 167-170°C are obtained.

EF: $C_{25}H_{29}N_5O_2$; MW 431.54

Elemental analysis:	calc.:	C 69.58	H 6.77	N 16.23
	fnd.:	C 69.50	H 6.92	N 16.38

Starting from starting compounds described below, the following is obtained according to the procedure in Example 2:

3. (+/-)-cis-9-Ethoxy-8-methoxy-6-[4-(2-p-methoxy-benzyl-2H-tetrazol-5-yl)phenyl]-1,2,3,4,4a,10b-hexahydrophenanthridine

M.p.: solidified oil

EF: $C_{31}H_{33}N_5O_3$; MW 523.62

Elemental

analysis x 0.3 H_2O:	calc.:	C 70.38	H 6.40	N 13.24
	fnd.:	C 70.67	H 6.57	N 12.97

4. (-)-cis-8,9-Dimethoxy-6-[4-(2-ethyl-2H-tetrazol-5-yl)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridine

M.p.: solidified oil

EF: $C_{24}H_{27}N_5O_2$; MW 417.52

Elemental

analysis x 0.12 H_2O:	calc.:	C 68.62	H 6.55	N 16.67
	fnd.:	C 68.63	H 6.81	N 16.59

Specific rotation: $[\alpha]_D^{20}$ = -75.2° (c=2, ethanol)

Starting compounds

A1. (+/-)-cis-9-Ethoxy-8-methoxy-6-[4-cyanophenyl]-1,2,3,4,4a,10b-hexahydrophenanthridine

5.1 g of (+/-)-cis-N-[2-(3-ethoxy-4-methoxyphenyl)-cyclohexyl]-4-cyanobenzamide (compound A5) are dissolved in 100 ml of acetonitrile and 3 ml of phosphorus oxychloride and the solution is stirred at 50°C for 8 h. The reaction mixture is added to 100 ml of saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase is washed with sodium hydrogencarbonate solution and water, dried using sodium sulfate and concentrated. 4.3 g of the title compound are obtained as solidified oil.

A2. (+/-)-cis-N-[2-(3-Ethoxy-4-methoxyphenyl)-cyclohexyl]-4-(2-ethyl-2H-tetrazol-5-yl)benzamide

5.0 g of (+/-)-cis-2-ethoxy-1-methoxy-4-(2-amino-cyclohexyl)benzene (compound B1) are dissolved in 60 ml of methylene chloride and 5.3 ml of triethylamine. A solution of 7.4 g of 4-(2-ethyl-2H-tetrazol-5-yl)benzoyl chloride in 60 ml of methylene chloride is added dropwise at RT, and the mixture is

extracted after stirring overnight with 100 ml each of water, 2N hydrochloric acid, saturated sodium hydrogencarbonate solution and water again. The organic phase is dried using sodium sulfate and concentrated. The residue is chromatographed on silica gel using a mixture of toluene/dioxane in the ratio 10/1. After concentration of the product fractions, 3.6 g of the title compound of m.p. 157-159°C are obtained.

Starting from starting compounds described below, the following is obtained according to the procedure described in Example A2:

A3. (+/-)-cis-N-[2-(3-Ethoxy-4-methoxyphenyl)-cyclohexyl]-4-(2-p-methoxybenzyl-2H-tetrazol-5-yl)benzamide

M.p.: 176-179°C

A4. (-)-cis-N-[2-(3,4-Dimethoxyphenyl)cyclohexyl]-4-(2-ethyl-2H-tetrazol-5-yl)benzamide

M.p. solidified oil

Optical rotation: $[\alpha]_D^{20}$ = -195.5° (c=0.2, ethanol)

A5. (+/-)cis-N-2-[3-Ethoxy-4-methoxyphenyl)cyclohexyl]-4-cyanobenzamide

M.p. solidified oil

B1. (+/-)-cis-2-Ethoxy-1-methoxy-4-(2-aminocyclohexyl)benzene

40.0 g of (+/-)-cis-2-ethoxy-1-methoxy-4-(2-nitro-cyclohex-4-enyl)benzene (compound C1) are dissolved in 1000 ml of ethanol and 500 ml of tetrahydrofuran, treated with 10 g of Raney nickel and hydrogenated at a hydrogen pressure of 100 bar for 4 days in an autoclave. After filtration and removal of the solvent in vacuo, 35.9 g of the title compound are obtained as a solidifying oil.

B2. (+/-)-cis-1,2-Dimethoxy-4-(2-aminocyclohexyl)benzene

8.5 g of (+/-)-cis-1,2-dimethoxy-4-(2-nitrocyclohexyl)benzene are dissolved in 400 ml of methanol and treated with 7 ml of hydrazine hydrate and 2.5 g of Raney nickel in portions at RT in the course of 8 h. After stirring overnight at RT, the reaction mixture is filtered, the filtrate is concentrated and the residue is chromatographed on silica gel using a mixture of toluene/ethyl acetate/triethylamine = 4/2/0.5. The title compound is obtained as an oil.

B3. (-)-cis-1,2-Dimethoxy-4-(2-aminocyclohexyl)benzene

12.0 g of (+/-)-cis-1,2-dimethoxy-4-(2-aminocyclohexyl)benzene and 6.2 g of (-)-mandelic acid are dissolved in 420 ml of dioxane and 60 ml of tetrahydrofuran and the solution is stirred at RT overnight. The solid is filtered off with suction, dried, treated with 100 ml of saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase is dried using sodium sulfate and concentrated under reduced pressure. 4.8 g of the title compound of m.p.: 80-81.5°C are obtained.

Specific rotation: $[\alpha]_D^{20}$ = -58.5° (c=1, ethanol)

C1. (+/-)-cis-2-Ethoxy-1-methoxy-4-(2-nitrocyclohex-4-enyl)benzene

89.25 g of (+/-)-trans-2-ethoxy-1-methoxy-4-(2-nitrocyclohex-4-enyl)benzene (compound D1) and 37 g of potassium hydroxide are dissolved in 500 ml of absolute ethanol. A solution of 23.5 ml of conc. sulfuric acid in 120 ml of absolute ethanol is then added dropwise such that the internal temperature does not exceed -2°C. After stirring for 1 h, the mixture is added to 4 l of ice water, and the precipitate is filtered off with suction, washed with water and dried. M.p.: 66-67°C.

C2. (+/-)-cis-1,2-Dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene

10.0 g of (+/-)-trans-1,2-dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene and 20.0 g of potassium hydroxide are dissolved in 150 ml of ethanol and 35 ml of dimethyl formamide. A solution of 17.5 ml of conc. sulfuric acid in 60 ml of ethanol is then added dropwise such that the internal temperature does not exceed 4°C. After stirring for 1 h, the mixture is added to 1 l of ice water, the precipitate is filtered off with suction, washed with water and dried, and the crude product is recrystallized from ethanol. 8.6 g of the title compound of m.p. 82.5-84°C are obtained.

C3. (+/-)-cis-1,2-Dimethoxy-4-(2-nitrocyclohexyl)benzene

8.4 g of (+/-)-cis-1,2-dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene are dissolved in 450 ml of methanol, treated with 2 ml of conc. hydrochloric acid and hydrogenated after addition of 500 mg of 10% strength Pd/C. The reaction mixture is filtered and the filtrate is concentrated. M.p.: 84-86.5°C.

D1. (+/-)-trans-2-Ethoxy-1-methoxy-4-(2-nitrocyclohex-4-enyl)benzene

110 g of 3-ethoxy-2-methoxy-ω-nitrostyrene (compound E1) and 360 mg of hydroquinone are suspended in 360 ml of absolute toluene and treated at -70°C with 180 ml of liquid 1,3-butadiene. The mixture is stirred at 160-180°C for 6 days in an autoclave and then cooled. The product is extracted by stirring with ethanol, filtered off with suction and dried. M.p.: 130-131°C.

D2. (+/-)-trans-1,2-Dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene

50.0 g of 3,4-dimethoxy-ω-nitrostyrene and 1.0 g (9.1 mmol) of hydroquinone are suspended in 200 ml of abs. toluene and treated at -70°C with 55.0 g (1.02 mmol) of liquid 1,3-butadiene. The mixture is stirred at 160°C for 6 days in an autoclave and then cooled. Some of the solvent is removed on a rotary evaporator, and the resulting precipitate is filtered off with suction and recrystallized in ethanol. M.p.: 113.5-115.5°C.

E1. 3-Ethoxy-2-methoxy-ω-nitrostyrene

236 g of 3-ethoxy-2-methoxybenzaldehyde, 101 g of ammonium acetate and 320 ml of nitromethane are heated to 100°C for 4 h in 655 ml of glacial acetic acid. The solution is added to 5 l of ice water, and the precipitate is filtered off with suction, washed with water and dried. M.p.: 132-133°C.

E2. 3,4-Dimethoxy-ω-nitrostyrene

207.0 g of 3,4-dimethoxybenzaldehyde, 100.0 g of ammonium acetate and 125 ml of nitromethane are heated to boiling for 3-4 h in 1.0 l of glacial acetic acid. After cooling in an ice bath, the precipitate is filtered off with suction, rinsed with glacial acetic acid and petroleum ether and dried. M.p.: 140-141°C. Yield: 179.0 g.

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to medicaments for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries, e.g. in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95%.

The person skilled in the art is familiar with auxiliaries which are suitable for the desired pharmaceutical formulations on account of his expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters, can be used.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation. To do this, these are either administered directly as a powder (preferably in micronized form) or by atomizing solutions or suspensions which contain them. With respect to the preparations and administration forms, reference is made, for example, to the details in European Patent 163 965.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those medicaments which are suitable for topical application. For the production of the medicaments, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The medicaments according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarly between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

In the investigation of PDE 4 inhibition on the cellular plane, the activation of inflammatory cells is ascribed particular importance. An example is FMLP (N-formyl-methionyl-leucyl-phenylalanine)-induced superoxide production of neutrophilic granulocytes, which can be measured as luminol-amplified chemiluminescence. (Mc Phail LC, Strum SL, Leone PA and Sozzani S, The neutrophil respiratory burst mechanism. In "Immunology Series" 57: 47-76, 1992; ed. Coffey RG (Marcel Decker, Inc., New York-Basel-Hong Kong)).

Substances which inhibit chemiluminescence and cytokine secretion and the secretion of proinflammatory mediators on inflammatory cells, in particular neutrophilic and eosinophilic granulocytes, T-lymphocytes, monocytes and macrophages are those which inhibit PDE 4. This isoenzyme of the phosphodiesterase families is particularly represented in granulocytes. Its inhibition leads to an increase in the intracellular cyclic AMP concentration and thus to the inhibition of cellular activation. PDE 4 inhibition by the substances according to the invention is thus a central indicator for the suppression of inflammatory processes. (Giembycz MA, Could isoenzyme-selective phosphodiesterase inhibitors render bronchodilatory therapy redundant in the treatment of bronchial asthma?. Biochem Pharmacol 43: 2041-2051, 1992; Torphy TJ et al., Phosphodiesterase inhibitors: new opportunities for treatment of asthma. Thorax 46: 512-523, 1991; Schudt C et al., Zardaverine: a cyclic AMP PDE 3/4 inhibitor. In "New Drugs for Asthma Therapy", 379-402, Birkhäuser Verlag Basel 1991; Schudt C et al., Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca; Naunyn-Schmiedebergs Arch Pharmacol 344; 682-690, 1991; Tenor H and Schudt C, Analysis of PDE isoenzyme profiles in cells and tissues by pharmacological methods. In „Phophodiesterase Inhibitors", 21-40, „The Handbook of Immunopharmacology", Academic Press, 1996; Hatzelmann A et al., Enzymatic and functional aspects of dual-selective PDE3/4-Inhibitors. In „Phosphodiesterase Inhibitors", 147-160, „The Handbook of Immunopharmacology", Academic Press, 1996.

1. Inhibition of PDE 4 activity

Methodology

The activity test was carried out by the method of Bauer and Schwabe, which was adapted to microtiter plates (Naunyn-Schmiedeberg's Arch. Pharmacol. **1980**, 311, 193-198). In this connection, the PDE reaction is carried out in the first step. In a second step, the resultant 5'-nucleotide is cleaved to give the uncharged nucleoside by a 5'-nucleotidase of the snake venom from Crotalus atrox. In the third step, the nucleoside is separated from the remaining charged substrate on ion exchange columns. The columns are eluted with 2 ml of 30 mM ammonium formate (pH 6.0) directly into minivials to which 2 ml of scintilation fluid is additionally added for counting.

The inhibitory values determined for the compounds according to the invention [inhibitory concentration as -log IC_{50} (mol/l)] follow from Table A below, in which the numbers of the compounds correspond to the numbers of the examples.

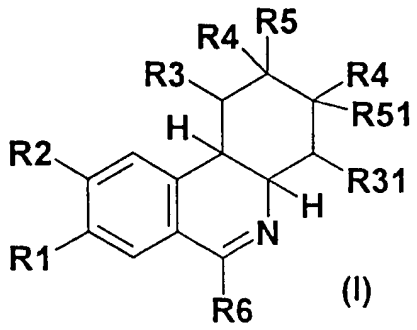
Table A

Inhibition of the PDE 4 activity

Compound	-log IC_{50}
2	8.78

Patent claims

1. A compound of the formula I



(I)

in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-2C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,

R31 is hydrogen or 1-4C-alkyl,

or in which

R3 and R31 together are a 1-4C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together are an additional bond,

R6 is a phenyl radical substituted by R7, where

R7 is a tetrazol-5-yl radical substituted by a radical R8, where

R8 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl or Ar-1-4C-alkyl, where

Ar is a phenyl radical which is unsubstituted or substituted by R9 and/or R10, and

R9 and R10 independently of one another are halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl or 1-4C-alkoxy,

or the salts of this compound.

2. A compound of the formula I as claimed in claim 1, in which

R1 is 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

or in which

R3 and R31 together are a 1-2C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together are an additional bond,

R6 is a phenyl radical substituted by R7, where

R7 is a tetrazol-5-yl radical substituted by a radical R8, where

R8 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl or Ar-1-4C-alkyl, where

Ar is a phenyl radical which is unsubstituted or substituted by R9 and/or R10, and

R9 and R10 independently of one another are 1-4C-alkyl or 1-4C-alkoxy,

or the salts of this compound.

3. A compound of the formula I as claimed in claim 1, in which

R1 is 1-4C-alkoxy, 3-7C-cycloalkoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-4C-alkoxy, 3-7C-cycloalkoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

or in which

R3 and R31 together are a 1-2C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together are an additional bond,

R6 is a phenyl radical substituted by R7, where

R7 is a tetrazol-5-yl radical substituted by a radical R8, where

R8 is hydrogen, 1-4C-alkyl, 5-7C-cycloalkyl, 3-7C-cycloalkylmethyl or Ar-1-2C-alkyl, where
Ar is a phenyl radical which is unsubstituted or substituted by R9, and
R9 is 1-2C-alkyl or 1-2C-alkoxy,
or the salts of this compound.

4. A compound of the formula I as claimed in claim 1, in which
R1 is 1-4C-alkoxy,
R2 is 1-4C-alkoxy,
R3 is hydrogen,
R31 is hydrogen,
R4 is hydrogen,
R5 is hydrogen,
R51 is hydrogen,
R6 is a phenyl radical substituted by R7, where
R7 is a tetrazol-5-yl radical substituted by R8, where
R8 is hydrogen, 1-4C-alkyl or 4-methoxybenzyl,
or the salts of this compound.

5. A compound of the formula I as claimed in claim 1, in which
R1 is methoxy or ethoxy,
R2 is methoxy or ethoxy,
R3 is hydrogen,
R31 is hydrogen,
R4 is hydrogen,
R5 is hydrogen,
R51 is hydrogen,
R6 is a phenyl radical substituted by R7, where
R7 is a 2H-tetrazol-5-yl radical substituted by R8, where
R8 is hydrogen, ethyl or 4-methoxybenzyl,
or the salts of this compound.

6. A compound of the formula I as claimed in claim 1 for use in the treatment of diseases.

7. A medicament comprising at least one compound of the formula I as claimed in claim 1 together with pharmaceutical auxiliaries and/or excipients.

8. The use of compounds of the formula I as claimed in claim 1 for the production of medicaments for the treatment of airway disorders.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 98/04477

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/00 C07D401/10 A61K31/44 C07D491/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 490 823 A (SANDOZ LTD ;SANDOZ AG (DE); SANDOZ AG (AT)) 17 June 1992 see the whole document ---	1-8
A	LUGNIER C ET AL: "Analysis of the specificity of inhibitors against some cyclic phosphodiesterases by multiparametric techniques" PHARMAZIE (PHARAT,00317144);92; VOL.47 (1); PP.46-9, XP002050965 UNIV. LOUIS PASTEUR;LAB. PHARMACOL. CELL. MOL.; STRASBOURG; FR. (FR) see Tableau 1 --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 1998	11/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 092, no. 3, 21 January 1980 Columbus, Ohio, US; abstract no. 015223, VAN INWEGEN R G ET AL: "Dihydro- and tetrahydroisoquinolines as inhibitors of cyclic nucleotide phosphodiesterases from dog heart. Structure-activity relations" XP002050966 see abstract & BIOCHEM. PHARMACOL. (BCPCA6,00062952);79; VOL.28 (8); PP.1307-12, USV PHARM. CORP.;TUCKAHOE; NY; USA	1-8
A	PALFREYMAN M N ET AL: "1 PHOSPHODIESTERASE TYPE IV INHIBITORS" PROGRESS IN MEDICINAL CHEMISTRY, vol. 33, 1996, pages 1-52, XP000650817 see page 25	1-8
A	SUGASAWA S ET AL: "SYNTHESE PARTIELL HYDRIERTER PHENANTHRIDIN-DERIVATE" BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, vol. 4, 1 January 1939, pages 675-678, XP000196051 see the whole document	1-8
A	CHEMICAL ABSTRACTS, vol. 117, no. 3, 20 July 1992 Columbus, Ohio, US; abstract no. 26304m, BOBOWSKI ET AL.: "1,4,4a,10b-Tetrahydro-N,N-dimethyl-4-phen antridinamidnes and ..." XP002050967 & J. Heterocycl. Chem. 1992, 29(1), 33-49 see abstract	1-8
P,X	WO 97 35854 A (BYK GULDEN LOMBERG CHEM FAB ;GUTTERER BEATE (DE)) 2 October 1997 see the whole document	1-8
P,X	WO 97 28131 A (BYK GULDEN LOMBERG CHEM FAB ;GUTTERER BEATE (DE)) 7 August 1997 see the whole document	1-8

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[illegible]pplication No
PCT/EP 98/04477

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0490823 A	17-06-1992	AT 145201 T	15-11-1996
		AU 643575 B	18-11-1993
		AU 8898591 A	18-06-1992
		CA 2057524 A	14-06-1992
		CS 9103757 A	17-06-1992
		DE 69123124 D	19-12-1996
		DE 69123124 T	15-05-1997
		DK 490823 T	17-02-1997
		ES 2093694 T	01-01-1997
		FI 915844 A	14-06-1992
		GR 3022034 T	31-03-1997
		IL 100328 A	08-12-1995
		JP 2042806 C	09-04-1996
		JP 4275276 A	30-09-1992
		JP 7064820 B	12-07-1995
		MX 9102502 A	01-06-1992
		PL 168329 B	29-02-1996
		PT 99775 A	30-11-1992
		RU 2060992 C	27-05-1996
		US 5177085 A	05-01-1993
		ZA 9109858 A	14-06-1993
WO 9735854 A	02-10-1997	DE 19613091 A	09-10-1997
		AU 2291097 A	17-10-1997
WO 9728131 A	07-08-1997	DE 19603321 A	07-08-1997
		AU 1719997 A	22-08-1997
		NO 983505 A	11-09-1998